P53 Regulates Rapid Apoptosis in Human Pluripotent Stem Cells.

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Public Summary:
Human pluripotent stem cells (hPSCs) are sensitive to DNA damage and undergo rapid apoptosis compared to their differentiated progeny cells. Here, we explore the underlying mechanisms for the increased apoptotic sensitivity of hPSCs that helps to determine pluripotent stem cell fate. Apoptosis was induced by exposure to actinomycin D, etoposide, or tunicamycin, with each agent triggering a distinct apoptotic pathway. We show that hPSCs are more sensitive to all three types of apoptosis induction than are lineage-non-specific, retinoic-acid-differentiated hPSCs. Also, Bax activation and pro-apoptotic mitochondrial intermembrane space protein release, which are required to initiate the mitochondria-mediated apoptosis pathway, are more rapid in hPSCs than in retinoic-acid-differentiated hPSCs. Surprisingly, Bak and not Bax is essential for actinomycin-D-induced apoptosis in human embryonic stem cells. Finally, P53 is degraded rapidly in an ubiquitin-proteasome-dependent pathway in hPSCs at steady state but quickly accumulates and induces apoptosis when Mdm2 function is impaired. Rapid degradation of P53 ensures the survival of healthy hPSCs but avails these cells for immediate apoptosis upon cellular damage by P53 stabilization. Altogether, we provide an underlying, interconnected molecular mechanism that primes hPSCs for quick clearance by apoptosis to eliminate hPSCs with unrepaired genome alterations and preserves organismal genomic integrity during the early critical stages of human embryonic development.

Scientific Abstract:
Human pluripotent stem cells (hPSCs) are sensitive to DNA damage and undergo rapid apoptosis compared to their differentiated progeny cells. Here, we explore the underlying mechanisms for the increased apoptotic sensitivity of hPSCs that helps to determine pluripotent stem cell fate. Apoptosis was induced by exposure to actinomycin D, etoposide, or tunicamycin, with each agent triggering a distinct apoptotic pathway. We show that hPSCs are more sensitive to all three types of apoptosis induction than are lineage-non-specific, retinoic-acid-differentiated hPSCs. Also, Bax activation and pro-apoptotic mitochondrial intermembrane space protein release, which are required to initiate the mitochondria-mediated apoptosis pathway, are more rapid in hPSCs than in retinoic-acid-differentiated hPSCs. Surprisingly, Bak and not Bax is essential for actinomycin-D-induced apoptosis in human embryonic stem cells. Finally, P53 is degraded rapidly in an ubiquitin-proteasome-dependent pathway in hPSCs at steady state but quickly accumulates and induces apoptosis when Mdm2 function is impaired. Rapid degradation of P53 ensures the survival of healthy hPSCs but avails these cells for immediate apoptosis upon cellular damage by P53 stabilization. Altogether, we provide an underlying, interconnected molecular mechanism that primes hPSCs for quick clearance by apoptosis to eliminate hPSCs with unrepaired genome alterations and preserves organismal genomic integrity during the early critical stages of human embryonic development.